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L3 ANSWER 1 OF 1 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 1997-231144 [21] WPIDS
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TI Tablets with rapid disintegration in oral cavity - prepared by compressing and moulding mixture of medicine, crystalline cellulose, hydroxypropyl-cellulose and lubricant.
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PA (RYUK-N) RYUKAKUSAN KK
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ADT JP--09071523 A 1995JP-0264583 19950907
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AN 1997-231144 [21] WPIDS
AB JP 09071523 A UPAB: 19970522
Tablets with rapid disintegration in the oral cavity are prepd. by compression and moulding a mixt. of a medicine, crystalline cellulose, lowly substd. hydroxypropylcellulose and a lubricant. Crystalline cellulose and lowly substd. hydroxypropylcellulose are used at ratios of 1:2 3-9.

Medicines which require rapid absorption (e.g. antihypertensive agents, cerebral circulation improving agents and anti-motion sickness agents are preferable used to prepare tablets.

USE - Used for chewable tablets.

ADVANTAGE - Rapid absorption of effective ingredients is obtained.

EXAMPLE - In an example, a compsn. of 10.0% meclozine HCL, 62.3% crystalline cellulose, 26.7% lowly substd. hydroxypropylcellulose and 1.0% Mg stearate was mixed and tabletted to give tablets. Tablets prepd. by compression pressure of 100, 200, 250 and 300 kgf showed disintegration period of 36.5, 27.3, 32.5, 40.1 and 54.0 sec., respectively.
Dwg.0/0

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WPI Acc No: 1997-231144/*199721*
XRAM Acc No: C97-074352
Tablets with rapid disintegration in oral cavity - prepared by compressing and moulding mixture of medicine, crystalline cellulose, hydroxypropyl-cellulose and lubricant
Patent Assignee: RYUKAKUSAN KK (RYUK-N)
Number of Countries: 001 Number of Patents: 001
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
JP 9071523	A	19970318	JP 95264583	A	19950907	199721	B

Priority Applications (No Type Date): JP 95264583 A 19950907
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
JP 9071523	A		5	A61K-009/20	

Abstract (Basic): JP 9071523 A
Tablets with rapid disintegration in the oral cavity are prepd. by compression and moulding a mixt. of a medicine, crystalline cellulose, lowly substd. hydroxypropylcellulose and a lubricant. Crystalline cellulose and lowly substd. hydroxypropylcellulose are used at ratios of 1:2 3-9.
Medicines which require rapid absorption (e.g. antihypertensive agents, cerebral circulation improving agents and anti-motion sickness agents are preferable used to prepare tablets.
USE - Used for chewable tablets.
ADVANTAGE - Rapid absorption of effective ingredients is obtained.
EXAMPLE - In an example, a compsn. of 10.0% meclozine HCL, 62.3% crystalline cellulose, 26.7% lowly substd. hydroxypropylcellulose and 1.0% Mg stearate was mixed and tabletted to give tablets. Tablets prepd. by compression pressure of 100, 200, 250 and 300 kgf showed disintegration period of 36.5, 27.3, 32.5, 40.1 and 54.0 sec., respectively.
Dwg.0/0
Title Terms: TABLET; RAPID; DISINTEGRATE; ORAL; CAVITY; PREPARATION; COMPRESS; MOULD; MIXTURE; MEDICINE; CRYSTAL; CELLULOSE; HYDROXYPROPYL; CELLULOSE; LUBRICATE
Derwent Class: A96; B07
International Patent Class (Main): A61K-009/20
International Patent Class (Additional): A61K-047/38
File Segment: CPI
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S5 1 PN=JP 08310969
? T/5

5/5/1
DIALOG(R)File 352:Derwent WPI

(54)[Title of the invention] Tablet which is rapidly disintegrated in oral cavity

[Claims]

[Claim 1] A tablet which is rapidly disintegrated in oral cavity, which comprises a mixture of crystalline cellulose, slightly substituted hydroxypropylcellulose and lubricant, where in slightly substituted hydroxypropylcellulose and crystalline cellulose were mixed at 1:2.3 to 1:9 and compression-molded.

[Detailed description of the invention]

[0001]

[Technical field to which the invention belong] The present invention relates to the technical field of providing a composition of a rapidly disintegrating tablet which is immediately disintegrated by saliva in oral cavity or small amount of water without chewing and can be swallowed as it is or with water in oral cavity (hereinafter, referred to as rapidly disintegrating tablet) and a process for preparing the composition.

[0002]

[Prior art] As a preparation which can be taken without water, a chewable tablet is sold as a digestive medicine. This does not need drink such as water when it is taken, and this can be taken by immediately crunching in oral cavity when necessary. There can be found no preparation as a tablet which is rapidly

disintegrated without chewing in oral cavity and which allows a tablet to be easily swallowed.

[Problems to be solved by the invention]

[0003] Necessity of crunching at administration of the aforementioned chewable tablet is inconvenient to people having the small chewing ability such as senior. To patients having the small swallowing ability, a tablet which can be rapidly disintegrated in oral cavity and taken is useful.

[0004] The present invention was done from such the viewpoint and an object thereof is to provide a tablet which is rapidly disintegrated in a few tens seconds with saliva or small amount of water in oral cavity and is easily swallowed.

[0005] As a circumstance where the rapidly disintegrating tablet of the present invention is necessary, there are drugs which are required to be administered as a tablet without water, for example, motion sickness prevention drugs. In addition, the previous tablet requires that a patient having the little swallowing ability crushes the tablet and take it. The rapidly disintegrating tablet of the present invention is rapidly disintegrated in oral cavity, and is useful for a patient having the little swallowing ability to take the tablet. In particular, a rapidly disintegrating tablet is useful to a patient who can hardly swallow due to cerebral vascular disorder or bed ridden elderly patient. Examples of such the drug include a drug for hypertension and cerebral circulation and metabolism improving

drug.

[Means to solve the problems]

[0006] In order to solve the aforementioned problems, the present inventors adopted the following composition of an excipient and a disintegrating agent in a tablet.

[0007] That is, rapidly disintegrating tablet of the present invention is characterized in that slightly substituted hydroxypropylcellulose as a disintegrating agent and crystalline cellulose as an excipient are mixed at a ratio of 1:2.3 to 1:9, a lubricant is mixed therein and, if necessary, a coloring agent or the like is mixed therein, which is compression-molded into a tablet by compression.

[0008] As a drug to be contained in the rapidly disintegrating tablet of the present invention, meclizine hydrochloride which is a drug effective for treating motion sickness which has the antiemetic activity is useful. Examples of other drugs effective for treating motion sickness which has the antiemetic activity include, in addition to the aforementioned meclizine hydrochloride, dimenhydrinate, thielperazine, diphenhydramine salicylate+ diprophylline, promethadinetheocrate. Examples of the drug for hypertension include captopril, cilazapril, enarapril maleate and riconopril. Examples of the cerebral circulation and metabolism improving drug include drug cinarezine, vinpocetine, brovinecamine fumarate, pentoxifylline, cinepazied maleate,

trapidil, nicardipine hydrochloride, flunarizine hydrochloride, mecrophenoxate and ifenprodil tartrate.

[0009] The present invention will be explained below.

[0010] <1> Process for preparing the rapidly disintegrating tablet of the present invention

1) Composition

The present invention is characterized in that a rapidly disintegrating tablet is made by using following excipients and disintegrating agents which are generally used:

(1) Crystalline cellulose (excipient) (manufacture by Asahi Kasei Kogyo, Avicel PH-102, particle diameter 100 μm)

(2) Slightly substituted hydroxypropylcellulose (disintegrating agent)

(manufactured by Shientsu Kagaku Kogyo, L-HPC, particle diameter 160 μm, Japanese Pharmacopoeia 12th edition)

[0011] 2)Ratio of incorporation in the rapidly disintegrating tablet of the present invention

(1) Rapidly disintegrating tablet containing no drug

A mixture of 1% of magnesium stearate (lubricant:manufactured by Wakojunyaku Kogyo MS, particle diameter 70 μm), and each 99% or more of a mixture obtained by mixing slightly substituted hydroxypropylcellulose and crystalline cellulose at a ratio of 1:2.3 to 1:9, is used as an agent for compression.

[0012] (2) Rapidly disintegrating tablet containing a drug (meclizine hydrochloride)

A mixture of 10% of meclizine hydrochloride (antiemetic agent: manufacture by Nihonbulkyakuhin, molecular weight 481.89, melting point 270°C (dec.)), 1% of magnesium stearate, and 89% or more of a mixture obtained by mixing slightly substituted hydroxypropylcellulose and crystalline cellulose at a ratio of 1:4, is used as an agent for compression.

[0013] 3) Compression conditions for rapidly disintegrating tablet of the present invention

A tablet was prepared under the following conditions. Generally, it is said that a more molding load is applied, a hardness of a tablet grows larger, leading to difficult disintegration. However, in the rapidly disintegrating tablet of the present invention, there can be obtained a rapidly disintegrating tablet having a hardness at a molding load of 100 to 300 kgf (hereinafter, referred to as compression pressure).

Apparatus: N-20E-type double-press powder compressing machine (manufactured by Okadaseikou) pestle diameter 8.0 mm, radius of curvature 10R

Tablet weight: 200 mg

Compression pressure: 100 to 300 kgf

[0014] <2> Conditions under which effects of the rapidly disintegrating tablet of the present invention are measured

1) Measurement of tablet hardness

When a tablet has not a hardness to a some degree (hereinafter,

referred to as hardness), the tablet retains no original shape. The tablet is required that it has a hardness at a suitable compression pressure but is rapidly disintegrated. For this, a hardness was measured. In measurement of a sold plain tablet described below, that tablet had a hardness of 13 to 15 Kg. The rapidly disintegrating tablet of the present invention had the same level of a hardness.

Semiautomated hardness tester (TS-50 N-type, manufactured by Okadaseikou)

The stress required for compression breakage is measured and this is adopted as hardness (kg).

[0015] 2) Disintegrating property of a tablet

The disintegrating property of the rapidly disintegrating tablet was measured by a substitute test described below. The results of this test is correlated with the actual results in oral cavity. All of the rapidly disintegrating tablets of the present invention were disintegrated in 74 seconds as shown in Examples. A tablet is completely or partially soaked in water in a small-type laboratory dish. Since motion of tongue adds to disintegration in oral cavity, a disintegrating time was measured by adding weak shaking to this small-type laboratory dish.

Shaking machine SA-31-type (manufactured by Yamato Scientific)

Vibration distance, 4 cm

Shaking times: 40/min. = 1/1.5 seconds (minimum setting value)

[0016] Using a sold plain tablet A (weight 200 mg, diameter 8 mm) and B (weight 280 mg, diameter 9 mm) having the almost same size as that of the rapidly disintegrating tablet (weight 200 mg, diameter 8 mm) of the present invention, a test was performed under the aforementioned condition, and the results thereof are shown in Table 1. It is clear that these sold plain tablets can not said to be a rapidly disintegrating tablet. The rapidly disintegrating tablet of the present invention is remarkably different from sold plain tablets.

Table 1

	Weight (mg)	Diameter (mm)	Hardness (km)	Disintegrating test (Japanese Pharmacopoeia)	Disintegrating time Laboratory dish method
Sold tablet A	200	8	4.0	Satisfactory (10 min.)	Retained original shape even after 1 hour.
Sold tablet B	280	9	16.5		Partially disintegrated by 1 hour

[0017]

[Examples] The present invention will be specifically explained by way of Examples below.

[0018]

[Example 1] Ratio of slightly substituted hydroxypropylcellulose and crystalline cellulose to be incorporated of 3:7 (when slightly substituted hydroxypropylcellulose 1, 1:2.3 in obtained).

Ingredient

Crystalline cellulose	69.3%
Slightly substituted hydroxypropylcellulose	29.7%
Magnesium stearate	1.0%

The aforementioned powders were uniformly mixed, which was compressed with a compression machine. The better relationship between disintegrating time, compression pressure and hardness was obtained as shown in Table 2.

Table 2 Average of n=3

Compression pressure (kgf)	100	150	200	250	300
Hardness (kg)	5.5	7.8	10.1	14.1	15.3
Disintegrating time (sec)	25.3	31.4	33.1	47.7	56.1

[0019]

[Example 2] Ratio of slightly substituted hydroxypropylcellulose and crystalline cellulose of 1:3.5

Ingredient	Amount
Crystalline cellulose	77.0%
Slightly substituted hydroxypropylcellulose	22.0%
Magnesium stearate	1.0%

The aforementioned powders were uniformly mixed, which was compressed with a compression machine. The better relationship between disintegrating time, compression pressure and hardness was obtained as shown in Table 3.

Table 3 Average of n=3

Compression pressure (kgf)	100	150	200	250	300
Hardness (kg)	4.7	7.1	8.9	11.7	14.5
Disintegrating time (sec)	31.7	36.8	40.3	58.2	73.7

[0020]

[Example 3] Ratio of slightly substituted hydroxypropylcellulose and crystalline cellulose of 1:4

Ingredient	Amount
Crystalline cellulose	79.2%
Slightly substituted hydroxypropylcellulose	19.8%
Magnesium stearate	1.0%

The aforementioned powders were uniformly mixed, which was compressed with a compression machine. The better relationship between disintegrating time, compression pressure and hardness was obtained as shown in Table 4.

Table 4 Average of n=3

Compression pressure (kgf)	100	150	200	250	300
Hardness (kg)	5.7	8.3	11.7	14.1	17.0
Disintegrating time (sec)	27	28.6	29.2	32.7	40.7

[0021]

[Example 4] Ratio of slightly substituted hydroxypropylcellulose and crystalline cellulose of 1:8

Ingredient	Amount
Crystalline cellulose	88.0%
Slightly substituted hydroxypropylcellulose	11.0%
Magnesium stearate	1.0%

The aforementioned powders were uniformly mixed, which was compressed with a compression machine. The better

relationship between disintegrating time, compression pressure and hardness was obtained as shown in Table 5.

Table 5 Average of n=3

Compression pressure (kgf)	100	150	200	250	300
Hardness (kg)	5.9	9.7	11.6	13.7	15.6
Disintegrating time (sec)	23.3	37.7	38.6	41.7	56.9

[0022]

[Example 5] Ratio of slightly substituted hydroxypropylcellulose and crystalline cellulose of 1:9

Ingredient	Amount
Crystalline cellulose	89.1%
Slightly substituted hydroxypropylcellulose	9.9%
Magnesium stearate	1.0%

The aforementioned powders were uniformly mixed, which was compressed with a compression machine. The better relationship between disintegrating time, compression pressure and hardness was obtained as shown in Table 6.

Table 6 Average of n=3

Compression pressure (kgf)	100	150	200	250	300
Hardness (kg)	5.2	8.8	11.3	14.6	18.0
Disintegrating time (sec)	22.3	35.6	42.8	27.2	36.2

[0023]

[Example 6]

Formulation in which meclizine hydrochloride is added 10% of meclizine hydrochloride as well as a ratio of slightly

substituted hydroxypropylcellulose and crystalline cellulose of 3:7 (when slightly hydroxypropylcellulose is 1, 1:2.3 is obtained).

Ingredient	Amount
Meclizine hydrochloride	10.0%
Crystalline cellulose	63.3%
Slightly substituted hydroxypropylcellulose	26.7%
Magnesium stearate	1.0%

The aforementioned powders were uniformly mixed, which was compressed with a compression machine. The better relationship between disintegrating time, compression pressure and hardness was obtained as shown in Table 7.

Table 7 Average of n=3

Compression pressure (kgf)	100	150	200	250	300
Hardness (kg)	3.4	4.6	6.2	7.8	11.8
Disintegrating time (sec)	36.5	27.36	32.5	40.1	54.0

[0024]

[Example 7]

Formulation in which meclizine hydrochloride is added 10% of meclizine hydrochloride as well as a ratio of slightly substituted hydroxypropylcellulose and crystalline cellulose of 1:4 .

Ingredient	Amount
Meclizine hydrochloride	10.0%
Crystalline cellulose	71.2%

Slightly substituted hydroxypropylcellulose	17.8%
Magnesium stearate	1.0%

The aforementioned powders were uniformly mixed, which was compressed with a compression machine. The better relationship between disintegrating time, compression pressure and hardness was obtained as shown in Table 8

Table 8 Average of n=3

Compression pressure (kgf)	100	150	200	250	300
Hardness (kg)	4.5	6.2	8.9	11.7	13.2
Disintegrating time (sec)	20.5	22.0	26.8	28.9	31.5

[0025]

[Example 8]

Formulation in which meclizine hydrochloride is added 10% of meclizine hydrochloride as well as a ratio of slightly substituted hydroxypropylcellulose and crystalline cellulose of 1:9.

Ingredient	Amount
Meclizine hydrochloride	10.0%
Crystalline cellulose	80.1%
Slightly substituted hydroxypropylcellulose	8.9%
Magnesium stearate	1.0%

The aforementioned powders were uniformly mixed, which was compressed with a compression machine. The better relationship between disintegrating time, compression pressure and hardness was obtained as shown in Table 9

Table 9 Average of n=3

Compression pressure (kgf)	100	150	200	250	300
Hardness (kg)	4.5	6.2	8.9	11.7	13.2
Disintegrating time (sec)	20.5	22.0	26.8	28.9	31.5

[0026]

[Effects of the invention] The rapidly disintegrating tablet of the present invention can provide a tablet which has a disintegrating time of 70 seconds or shorter in a disintegrating test using a small-type laboratory dish and is rapidly disintegrated in around a few tens second by saliva (small amount of water) in oral cavity. As a result, administration of a tablet to senior having the weak swallowing ability and administration of a tablet without no water become possible.

(57) [Abstract]

[Construction] In a composition of a tablet (referred to as rapidly disintegrating tablet) which is rapidly disintegrated by saliva (small amount of water) in oral cavity, a rapidly disintegrating tablet, which comprises a mixture of slightly substituted hydroxypropylcellulose as a disintegrating agent, crystalline cellulose as an excipient, and lubricant, wherein an incorporation ratio of slightly substituted propylcellulose and crystalline cellulose is 1:2.3 to 1:9.

[Effects] The aforementioned rapidly disintegrating tablet can provide a tablet which has a disintegrating time of 70 seconds or shorter in a disintegrating test using a small-type laboratory dish and rapidly disintegrated in a few seconds by saliva (small amount of water) in oral cavity. As a result, senior having no chewing ability can take the tablet, and one can take the tablet without water.

002219583
WPI Acc No: 1979-18758B/*197910*
Easily disintegrabl granules contg. pharmaceutical - and low substitution degree hydroxypropyl-cellulose, water-soluble binder and water
Patent Assignee: SHINETSU CHEM IND CO LTD (SHIE)
Number of Countries: 001 Number of Patents: 001
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week
JP 54011226	A	19790127				197910 B

特開昭 54-11226

Priority Applications (No Type Date): JP 7775090 A 19770624

Abstract (Basic): JP 54011226 A
Easily disintegrable granules comprise granulated mixt. of (a) 100 pts. wt. powdered main drug; (2) 2-20 pts. wt. low substitution degree hydroxypropylcellulose comprising particles of hydroxypropyl gp. substitution (mols) of 0.05 is approx. 1.00 per anhydrous glucose unit and diameter <105 um for >95% of the particles; (c) 0.1 is approx. 10 pts. wt. water soluble binder and (d) water.
As water soluble binder may be used natural prod. e.g. starch, acacia or gelatine, synthetic prod. as e.g. carboxymethylcellulose, methylcellulose, hydroxypropylcellulose, hydroxypropylmethylmethylcellulose, polyvinylpyrrolidone or PVA in an amt. of 1 is approx. 10 wt. % w.r.t. material powder.
Easily disintegrable granules may be produced using water solvent without problems of fire or explosion caused by organic solvent.
Title Terms: EASY; DISINTEGRATE; GRANULE; CONTAIN; PHARMACEUTICAL; LOW; SUBSTITUTE; DEGREE; HYDROXYPROPYL; CELLULOSE; WATER; SOLUBLE; BIND; WATER
Derwent Class: A96; B07
International Patent Class (Additional): A61K-009/16

SPECIFICATION

1. Title of the invention

Easily disintegrating granule

2. Claims

1. An easily disintegrating granule, which comprises a granulated mixture of (1) 100 parts by weight of a powdery basis raw material, (2) 2 to 20 parts by weight of a slightly substituted hydroxypropylcellulose powder in which a hydroxypropyl group substitution mole number per anhydrous glucose unit is 0.05 to 1.00 and which comprises particles, 95% by weight or more of which have a diameter of 105 μm or smaller, (3) 0.1 to 10 parts by weight of a water-soluble binder, and (4) water.

3. Detailed description of the invention

The present invention relates to an easily disintegrating granule.

Previously, in many cases, a granule has been prepared by a wet method, in which a solution of a binder is added to a powdery basis or a raw material powder containing a powdery basis, an excipient and the like, which is granulated. This wet method is further classified into extrusion granulation, oscillator granulation, rolling granulation and crushing granulation. Among them, an extrusion granulation method is generally used in which a binder solution is added to a raw material powder and, if necessary, a liquid is further added

to mix, which is extruded through a screen.

As a liquid used for adding the aforementioned solution, organic solvents such as acetone, methyl alcohol, ethyl alcohol and isopropyl alcohol, and water are used. However, these organic solvents are flammable and have a risk of fire and explosion. Also from a viewpoint of a price, exploitation of a method using only water is desired. In this case, when an amount of liquid to be added is small, granulation is not sufficiently performed. On the other hand, when the amount is too large, granules extruded through a screen adhere to each other. Therefore, it is necessary to determine a suitable range of addition in advance. However, depending upon the nature of a raw material powder, a suitable range of addition does not exist in a water solvent, that range is very narrow and a stable granule is not obtained. Upon extrusion granulation of such the raw material powder, a method is adopted in which a suitable organic solvent is used in place of water, or an excipient having the better granulating property, for example, lactose or starch is added at a large amount. However, the former has the defect described above. and latter can improve the granulating property and, on the other hand, has the defects that a rate of a basis ingredient to be contained becomes too low and the productivity is lowered.

On the other hand, it is known that slightly substituted

hydroxypropylcellulose which is a cellulose derivative is added to a solid drug as an excipient or a disintegrating agent (JP-B 46-42792, JT-B 48-38858). However, when this is added to a raw material powder to mix, which is granulated using water as a solvent without using any water-soluble binder, even a raw material having the worse granulating property can improve the granulating property. However, a granule obtained by this method has a very long disintegrating time in the living body, has the insufficient strength and, thus, a practical productivity can not be obtained frequently.

The present invention is to provide an easily disintegrating granule which solves such the problem, and relates to an easily disintegrating granule, which comprises a granulated mixture of (1) 100 parts by weight of a powdery basis raw material, (2) 2 to 20 parts by weight of a slightly substituted hydroxypropylcellulose powder in which a hydroxypropyl group substitution mole number per anhydrous glucose unit is 0.05 to 1.00 and which comprises particles, 95% by weight or more of which have a diameter of 105 μm or smaller, (3) 0.1 to 10 parts by weight of a water-soluble binder, and (4) water.

This will be explained. The present inventors found that, upon preparation of a granule by a method such as extrusion granulation and the like, by adding slightly substituted hydroxypropylcellulose to a raw material powder,

even a material to be granulated with difficulty can be easily granulated and, at the same time, by adding a water-soluble binder, the disintegrating property in the living body is remarkably improved, a granule having the excellent strength is obtained and, upon this, addition of only water is sufficient, which resulted in completion of the present invention.

When a water-soluble binder is added, a disintegrating time is generally delayed in the case of a tablet. However, it is an unexpected fact that, in the case of a granule, easily disintegrating property is obtained.

It is necessary that a slightly substituted hydroxypropylcellulose powder used in the present invention has a hydroxypropyl group substitution mole number per anhydrous glucose unit ranging 0.05 to 1.00. When the number is below this range, it is difficult to prepare a granule having the large strength. Conversely, when the number is above this range, the workability of extrusion granulation most generally used can be hardly improved. It is also necessary that the powder is a powder comprising particles, 95% by weight or more of which have a particle diameter of 105 μm or smaller, preferably 75 μm or smaller. When the powder is more coarse, clogging of a screen is caused and, not only a granulation rate is lowered, but also the smoothness of a granule surface is lost, leading to remarkable decrease

in the product value. When an amount to be added is too small, the effects of improving the granulating property and the granule strength can not be expected. When the amount is too large, since the content of a basis ingredient is lowered, such the amount is an amount corresponding to 2 to 20% by weight, preferably 3 to 15% by weight relative to a raw material powder.

Many of medicaments are ionic and, when an additive is ionic, quality change of a medicament by a reaction is cared. In particular, when water is added to mix, this reaction is easily caused. However, since slightly substituted hydroxypropylcellulose is nonionic, there is any such the care at all and, thus, it can be applied to all medicaments.

Slightly substituted hydroxypropylcellulose used in the present invention has been previously known, and can be obtained by the known method, for example, by soaking a pulp into an aqueous sodium hydroxide solution having the concentration of 10 to 50%, squeezing it, reacting this and propylene oxide at 20 to 90°C for 2 to 8 hours, or reacting propylene oxide with a powdery pulp in an organic solvent such as isopropyl alcohol, t-butyl alcohol and hexane after addition of an aqueous sodium hydroxide solution, then neutralizing sodium hydroxide, which is purified, dried and crushed.

Examples of a water-soluble binder include natural

products such as starch, gum arabic and gelatin, and synthetic products such as carboxymethylcellulose, methylcellulose, hydroxymethylcellulose, hydroxypropylmethylmethylcellulose, polyvinylpyrrolidon and polyvinyl alcohol. These are used at a proportion of 1 to 10% by weight relative to a raw material powder. This binder is generally used after it is dissolved in water to be added at granulation, in advance. However, a powdery binder may be mixed with a raw material powder and slightly substituted hydroxypropylcellulose in advance and, thereafter, water may be added.

An amount of this water-soluble binder to be used is a range of 0.1 to 10 parts by weight, preferably 0.2 to 5 parts by weight relative to 100 parts by weight of a powdery basis raw material. This is because, when the amount to be used is too small, the disintegrating property which is the purpose of the present invention can not be improved and, when the amount is conversely too large, not only disintegration is delayed, but also the granule of the present invention has the adhering property and granulation becomes difficult.

In the practice of the present invention, previously known excipients such as lactose and sucrose may be used.

A powdery basis raw material used upon obtaining of the granule of the present invention is not particularly limited and includes a variety of raw material powders containing a powdery drug ingredient, or a basis ingredient with an

excipient, a bulking agent, a sweetener and other additive ingredients incorporated.

The granule of the present invention can be easily prepared by using slightly substituted hydroxypropylcellulose powder and a water-soluble binder at a relatively small amount, without use of an organic solvent, and without addition of a large amount of an excipient, even in the case of a raw material powder which has been previously difficult to be granulated with a water solvent. For this reason, there is no risk of burn and explosion due to an organic solvent and, furthermore, a granule having a high content of a basis ingredient can be obtained.

In addition, a this integrating time of a granule becomes remarkably short and, not only a rapid-acting drug can be prepared, but also the strength of a granule can be improved as compared with a method in which only slightly substituted hydroxypropylcellulose is added.

Then, Examples are illustrated. Part and % in respective Examples denote part by weight and % by weight, respectively. A disintegrating time and an abrasive wear were for a granule measured under the following conditions, respectively.

Disintegrating time:

Japanese Pharmacopoeia, 9th edition, general test method 33, disintegration test method (using tap water at 37°C)

Abrasive wear:

10 g of granules which had passed through a sieve having an opening of 840 micron and had not passed through a sieve having an opening of 350 micron were placed into a rotating tablet abrasive wear tester, which was rotated by 200 rotations (10 min.), classified through a 350 micron sieve, and a decrease rate in weight (%) of a granule was measured.

Example 1, Comparative Examples 1 to 3

95 parts of finely-divided aspirin, 5 parts of slightly substituted hydroxypropylcellulose having a size distribution shown in the following Table 1 and having a substitution mole number per anhydrous glucose unit of 0.30 and 25 parts of a 5% aqueous starch solution were mixed, which was granulated at a rate shown in the following Table 1 using a rotary-type extrusion granulator (screen diameter 12.5 cm, screen hole diameter 0.6 mm) manufactured by Nihonyakugyokikaisha. Then, the granule was dried with a venting dryer at a temperature of a 60°C, and classified using a sieve having an opening of 0.84 mm (JI8 standard net sieve).

A disintegrating time and an abrasive wear for granules which had passed through this sieve were examined, and the results thereof are shown in the following Table 1.

For comparison, the same composition except that slightly substituted hydroxypropylcellulose, 90% of which have a size distribution of 105 μm or smaller, was used

(Comparative Example 2), the same composition except that a 5% aqueous starch solution was not used at all (Comparative Example 3) and only finely-divided aspirin (Comparative Example 4) were subjected to granulation and sieving treatment, a disintegrating time and an abrasive wear of granules which had passed through a sieve are examined and the results thereof are also shown in the following Table 1.

When a 5% aqueous starch solution was not used at all, water was added at 30% (per unit weight of a mixed powder), and treatment was performed.

Table 1

		Example 1	Comparative Example 1	Comparative Example 2	Comparative Example 3
Particle size of additive (%)	105 - 149 μm	1	10	1	
	74 - 105 μm	6	15	6	
	74 μm or smaller	93	75	93	
Granulation rate (g/min)		110	30	100	Un-granulatable
Physical properties	Disintegrating time (min.)	1	3	16	
	Abrasive wear (%)	0.97	0.80	1.66	

Examples 2 to 3, Comparative Examples 4 to 5

A particle size of slightly substituting hydroxypropylcellulose having a hydroxypropyl group substitution mole number per anhydrous glucose unit shown in the following Table 2 was adjusted by classifying so that a particle diameter 74 μm or smaller is 96%, and a particle

diameter between 74 and 105 μm is 4%.

Then, 95 parts of finely-divided phenacetin, 5 parts of slightly substituted hydroxypropylcellulose adjusted above and 2 parts of TO-5 (trademane manufactured by Shinetuskagaku, hydroxypropylmethylcellulose) were mixed in a biaxial kneader for 10 minutes, water was added as shown in the following Table 2, mixed for 20 minutes, which was granulated with the same rotary-type extrusion granulator manufactured by Nihonyakugyokikai as that used in Example 1, then dried and classified.

A disintegrating time and an abrasive wear for granules which had passed through this sieve were examined by the method described above, and the results thereof are shown in the following Table 2.

For comparison, the same composition except that Avicel (tradeneme manufactured by Asahikasei, microchrystalline cellulose) was used in place of slightly substituted hydroxypropylcellulose (Comparative Example 4) and the same composition except that hydroxypropylcellulose having a hydroxyporpyl group substitution mole number of 1.53 was used (Comparative Example 5) were subjected to granulation, drying and classifying treatment as described above, a disintegrating time and an abrasive wear of granules which had passed through a sieve were examined, and the results are also shown in Table 2.

Table 2

		Comparative Example 4	Example 2	Example 3	Example 5
Additive		Avicel	Slightly substituted hydroxypropyl-cellulose	Same as left	Hydroxypropyl-cellulose
Hydroxypropyl group substitution mole number		0	0.20	0.71	1.53
Amount of water to be added (%)		2.5	2.6	2.4	Ungranulatable
Granulation rate (g/min)		110	120	120	
Physical properties	Disintegrating time (min.)	300	30	5	
	Abrasive wear (%)	1.9	0.8	1.0	

(Provided that, an amount of water to be added is a value per unit weight of a mixed powder)

Example 4, Comparative Example 6

Using slightly substituted hydroxypropylcellulose having a substitution mole number per anhydrous glucose unit of 0.22 which had passed through a 149 micron sieve and at a formulation in Table, a test of preparing a spherical granule was performed. First, phenacetin and slightly substituted hydroxypropylcellulose were mixed with a biaxial kneader for 5 hours, a 7% aqueous solution of HPO-SL (tradename manufactured by Nihonsoda, hydroxypropylcellulose) was added, stirred to mix for 5 hours, which was granulated at a rate shown in the following Table 3 using a biaxial extrusion granulator Pelsodable (EXD-60 type (screen hole diameter 1

mm) manufactured by Fujipowdal. Further, a granule was subjected to sphericalization treatment with Melizer Q-400 type manufactured by Fujipowdal, dried at 60°C, which was examined for a disintegrating time, an abrasive wear and appearance, and the results thereof are shown in Table 3.

The same treatment as that described above was performed using lactose and corn starch without addition of slightly substituted cellulose ether, a granule was examined for a disintegrating time, an abrasive wear and appearance, and the results are also shown in Table 3.

An abrasive wear was measured using granules having a particle diameter of 710 to 1410 μm by rotating an abrasive wear tester, and decrease in weight (%) was obtained at a sieve having an opening of 710 micron.

Table 3

No.		Example 4	Comparative Example 6
Formulation	Phenacetin	90 parts	54 parts
	Slightly substituted hydroxypropylcellulose	10 parts	–
	Lactose	–	36 parts
	Corn starch	–	10 parts
HPC-SL aqueous solution Added amount (%)		24	15
Granulation rate (Kg/hour)		40	52
Physical properties	Disintegrating time (sec)	60	90
	Abrasive wear (%)	0.2	1.1
Appearance of granule		Spherical	Slightly elongated